ORIGINAL ARTICLE

Cystic Fibrosis in Malaysian Children

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Summary

Cystic fibrosis (CF) is an autosomal recessive disease commonly found among the Caucasian population. The availability of sweat test and with increasing experience have made it possible to diagnose more cases of CF. Our first case of CF was diagnosed 16 years ago and to date we have managed sixteen cases of CF. Sixteen children were diagnosed with CF in our units at the Paediatric Institute and University Malaya Medical Centre (UMMC). They were referred with either one or all of the following symptoms: i) recurrent pneumonia, ii) bronchiectasis, iii) failure to thrive, iii) malabsorption or iv) history of meconium ileus obstruction during the neonatal period. When the clinical features suggested strongly of CF, sweat tests will be performed in duplicates and considered positive when the sweat chloride or sweat sodium was more than 60 mmol/l for both results. Seventy- two hours fecal fat excretion or stool for fat globule was performed to document malabsorption. From the year 1987 to 2003, 16 patients were confirmed to have cystic fibrosis in Malaysia by positive sweat tests. Thirteen patients were diagnosed in Paediatric Institute while the remaining three were diagnosed in UMMC. On follow-up two patients died due to severe bronchopneumonia at the age of two years old. Although once considered rare, CF should now be considered in any children with clinical presentations of recurrent chest infections, bronchiectasis, in the presence or absence of malabsoption stmptoms and in neonates with meconium ileus obstruction

Key Words: Cystic fibrosis, Malaysia, Malabsorption syndrome, Pancreatic enzymes, Meconium ileus obstruction

Introduction

Cystic fibrosis (CF) is an autosomal recessive disease commonly found among the Caucasian population. It is less common among the Asian population with an estimated prevalence among Asians to be 1 in 10,000 in the United Kingdom and 1 in 40,000 among Asians in the United States[1]. It has being reported to occur among the Indians, Pakistanis and Arabs[2]. We reported our first three Malay children with CF eight years ago[3].

It is a multi systemic disease that affects major organs such as the lung, liver, biliary tract and the bones. Patients die prematurely to respiratory failure. With aggressive treatment patients may survive slightly more than 30 years old. The final option of treatment is lung transplantation. In Malaysia these cases are once considered rare. However, with the availability of sweat testing facility, more cases of CF were diagnosed in our respiratory unit. To date sixteen cases were confirmed with sweat tests. This paper demonstrates their clinical presentations, diagnostic issues and our experience in managing these patients.

Materials and Methods

Sixteen patients that were seen in the respiratory units in Paediatric Institute and UMMC presented with history

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of recurrent pneumonia. They may be associated with one or all of the following symptoms i.e. i) bronchiectasis, ii) failure to thrive, iii) malabsorption or iv) history of meconium ileus obstruction during the neonatal period. A detailed history was taken and all these children were examined. Other differential diagnoses considered were immunodeficiency syndrome, gastro-oesophageal reflux, bronchiolitis obliterans, tuberculosis and primary ciliary dyskinesia.

Baseline haemoglobin and differential counts, liver function tests and renal profile were performed. Serum immunoglobulins were taken in all these patients. Oesophageal pH studies were only performed in patients with history of feeding problems such as choking, wheezing or coughing with feeds to exclude gastro-oesophageal reflux. Sweat tests were performed in patients with recurrent pneumonia with/out symptoms of malabsorption, bronchiectasis and in infants with meconium ileus obstruction. However, in patients presenting with recurrent pneumonia with symptoms of gastro-oesophageal reflux, sweat test was not performed. Sweat tests were performed in duplicates and considered positive when the sweat chloride or sweat sodium levels were more than 60 mmol/l for both results. The volume of sweat must be adequate i.e. 100 ml of sweat. Malabsorption was detected objectively either by testing the stools for fat globule or by performing 72 hours fecal fat excretion.

In the presence of malabsorption, the patients were started on pancreatic enzyme replacements. The enzymes were taken just before meals. i.e. one capsule /kg /day. A capsule of pancreatic enzyme contains Lipase 10,000 IU, Amylase 8000 IU and Protease 600 IU. For the younger children, the granules were sprinkled on food. Chest radiographs and high resolution computed tomograms were performed in all these patients. Features of bronchiectasis on the CT scans were tram line appearance, dilated and thickened airways and cystic changes. Parents were taught chest physiotherapy and breathing exercise. At home they were required to perform physiotherapy at least twice a day. In the older children we encouraged active participation in sport activities. Initially the patients will be seen monthly and once stable they will be seen every three months. If they are unwell, they will be seen earlier. Mild exacerbation of chest infections will be treated as outpatients with oral antibiotics for seven to ten days. Moderate to severe infection will be treated with intravenous antibiotics in the ward. Sputum culture and sensitivity will be obtained if they can expectorate and nasopharyngeal aspirates performed in the younger children.

In mild infection, the choice of antibiotics are oral cefuroxime axetil, ampicillin-clavulanate acid or ciprofloxacin. In moderate to severe infections, the first choice of antibiotics is intravenous ceftazidime and amikacin. Other choices are imipenam, piperacillin or ciprofloxacin. The duration of antibiotics given during hospitalisation is 14 days or longer depending on their clinical responses. The choices of antibiotics are individualised with sputum culture and sensitivity to assist in the decisions. If they are chronically unwell or continued to be colonized with Pseudomonas aeruginosa, they will be started on nebulised gentamicin 60 mg daily for three months. In newly diagnosed infants with CF they are given anti-staphylococcal i.e. oral cloxacillin up to two years old.

Chest physiotherapy is performed twice a day during the admission. In older children above children six years they are prescribed the Acapella, which is a vibratory positive expiratory pressure therapy (PEP) system, which provides a positive pressure throughout the exhalation process. This technique facilitates cough and expectoration of secretions from the chest. In the ward or at home they were required to do it three times a day in addition to the conventional therapy.

They are referred to the dietitian to ensure that adequate calories are taken. These children require normal calories with 20% extra to compensate for their increase energy expenditure. Their fat intake is normal. Since they have higher salt losses especially during the hot season, they are advised to drink oral rehydration salt solution and are allowed added salt to their food intake.

On follow-up, weight and height are measured to ensure adequate growth. They are assessed for exacerbation of chest infections such as increasing cough and sputum production. Stool frequency and abdominal pain are asked to exclude complications such as stetorrhoea due to inadequate pancreatic supplements and meconium ileus equivalent. The pancreatic supplements will be adjusted accordingly to their nutritional intake and also their stool frequency.

Results

From the year 1987 to 2003, 16 patients were confirmed to have cystic fibrosis by sweat testing. Three patients had meconium ileus obstruction during the neonatal period requiring surgical intervention. The oldest patient is 16 years old and the youngest being two years old. There are equal males and females being affected. There are nine Malays, four Indians, one of mixed parentage Chinese/Malay, one Chinese and one Iban patient. The age of diagnosis was between three months to six years old. Table I shows the demographic data of these patients.

At presentation all of them had failure to thrive. Eleven patients that were diagnosed later than one year old had history of recurrent pneumonia by the time they were referred to the unit. Nine of these patients had developed bronchiectasis. Twelve patients had associated malabsoption syndrome. Six patients had suffered from hyponatremic dehydration. Table II shows the various clinical presentations of these children. Two of them had older siblings with meconium ileus obstruction who died during the infancy period due to severe pneumonia. Patient No 6 suffered from rectal prolapse due to the untreated severe malabsorption. The rectal prolapse resolved when the malabsoption symptoms were treated with pancreatic supplements. On follow-up three patients died of severe bronchopneumonia within one year of diagnosis.

Lung function tests were performed in seven patients. Table III shows the lung function results in these children. Three patients had normal lung functions with FEV1 >80% predicted. Three patients had an obstructive component to their flow volume curve. One patient had restrictive lung function. We did not perform any body phletysmography to measure the lung volumes.

Table IV shows the results of the sweat tests, fecal fat excretion and the pattern of respiratory organism isolated from their respiratory secretions. Pseudomonas aeruginosa is the commonest respiratory pathogens isolated from the respiratory secretions.

Table I: Demographic data of CF patients

No	Name	Year diagnosed	Sex	Race	Age at diagnosis (months)	Current age (years)
1*	AM	1987	Male	Malay	3	16
2*	ASM	1996	Male	Malay	1.5	7
3**	LB	1993	Female	Malay	48	15
4**	AB	1993	Female	Malay	1.5	10
5	LA	1997	Male	Indian	60	12
6	NS	2001	Female	Malay	72	9
7	MS	2001	Male	Malay	5	Died
8	DH	2001	Male	Malay	3	1
9	NF	2001	Female	Malay	19	Died
10	AL	2002	Male	Iban	84	Died
11	TG	2002	Male	Indian	72	6
12	SF	2002	Female	Malay	72	6
13	BA	2002	Male	Indian	90	8
14	NDL	2001	Female	Malay/Chinese	5	2
15	RE	2001	Female	Indian	6	2
16	MQM	2003	Female	Chinese	9.2	10

1* and 2* are brothers. 3** and 4** are sisters.

Table II: Clinical Features of the CF patients

Patients	Recurrent pneumonia	Malabsorption at presentation	Failure to thrive	Clubbing	Bronchiectasis at presentation	Hyponatremic dehydration
AM	Yes	Yes	Yes	No	No	Yes
ASM	No	Yes	Yes	No	No	No
LB	Yes	Yes	Yes	Yes	Yes	Yes
AB	No	Yes	Yes	No	No	No
LA	Yes	Yes	Yes	Yes	Yes	Yes
NS	Yes	Yes	Yes	Yes	Yes	No
MS	Yes	Yes	Yes	No	Bronchiolitis obliterans	Yes
DH	No	Yes	Yes	No	Bronchiolitis obliterans	Yes
NF	Yes	Yes	Yes	No	Yes	Yes
AL	Yes	No	Yes	Yes	Yes	No
TG	Yes	No	No	Yes	Yes	No
SF	Yes	Yes	Yes	No	Yes	No
BA	No	Yes	Yes	Yes	Yes	No
NDL	No	Yes	Yes	No	No	No
RE	Yes	No	Yes	Yes	No	No
MQM	Yes	No	Yes	Yes	Yes	No

Table III: Lung Function of children with CF

Patients	Patients	Predicted (liters)	Pre-Bronchodilator	% Predicted	Post Bronchodilator	% Predicted
1:AM	FVC	3.43	3.57	104	3.58	104
	FEV1	3.15	3.16	100	3.27	104
	FEV1/FVC	86	88		92	
2:ASM	FVC	1.05	1.19	113	1.15	110
	FEV1	0.91	1.17	129	1.12	124
	FEV1/FVC	86	98		98	
3:LB	FVC	2.51	1.59	63	1.80	72
	FEV1	2.36	1.21	51	1.29	54
	FEV1/FVC	86	76		71	
4:AB	FVC	1.83	1.34	73	1.75	95
	FEV1	1.69	1.34	79	1.63	97
	FEV1/FVC	86	100		93	
5:LA	FVC	2.00	1.76	88	1.76	88
	FEV1	1.80	1.32	73	1.29	72
	FEV1/FVC	86		75	74	
6: TG	FVC	1.6	0.96	60	1.03	64
	FEV1	1.47	0.96	65	1.02	70
	FEV1/FVC	86		100	99	
7:MQM	FVC	2.49	0.59	24	0.55	22
	FEV1	2.11	0.5	23	0.47	22
	FEV1/FVC	90	84		86	

Table IV: Investigation results of CF patients

No	Patient	Sweat Test	Respiratory organism	Fecal fat excretion
1*	AM	Sodium 130 Chloride 80	Klebsiella MRSA	Positive fat globule
2*	ASM	Chloride 80 mmol/l	MRSA	Positive fat globule
3**	LB	Sodium 127 Chloride 110	Pseudomonas aeruginosa	Not done
4**	AB	Sodium 120 Chloride 72	Pseudomonas aeruginosa	Not done
5	LA	Sodium 142	Pseudomonas aeruginosa	Positive fat globule
6	NS	Chloride 118	Pseudomonas aeruginosa	38
7	MS	Chloride 142	Pseudomonas aeruginosa	88
8	DH	Chloride 101	Pseudomonas aeruginosa Sternotrophomonas maltophilia	Positive for fat globule
9	NF	Chloride 167	Pseudomonas aeruginosa	80
10	AL	Chloride 112	Staphylococcal aureus Pseudomonas aeruginosa	11
11	TG	Chloride 112	MRSA	14
12	SF	Chloride 118	No growth	Positive for fat globule
13	BA	Sodium 140 Sodium 135	Pseudomonas aeruginosa	Positive for fat globule
14	NDL	Sodium120 Sodium 115	Normal flora	Positive for fat globule
15	RE	Sodium 134 Sodium 133	Staphylococcal aureus Pseudomonas aeruginosa	Positive for fat globule
16	MWQ	Sodium 111 Sodium 116	Staphylococcal coagulase negative	0.2

Table IV: Investigation results of CF patients

No	Patients	Progress an outcome
1	AM	Currently he is attending Form Five. He weighs 50.8 kg with a height of 129cm. Both his height and weight are below the 3rd centiles.
2	ASM	Currently he is attending standard 2. His height is 111 cm and his weight is 17.3 kg. Both his height and weight are below thee 3rd centiles
3	LB	She is attending form four. She has not attained menarche. Her weight is 28.4 kg and her height is 143cm. Both her height and weight are below the third centilesis he Died in 2003 due Pseudomonas pneumonia.
4	AB	She is attending standard four. Her weight is 23.5kg and her height is 127 cm. Both her height and weight are below the third centiles.
5	LA	He is attending form one. He weighs 20.6kg and his height is 129 cm. Both his height and weight are below the third centiles.
6	NS	She is attending standard four. Her height is 111cm and his weight is 17.3kg. Both her height and weight are below the third centiles.

No	Patients	Progress an outcome
7	MS	He died in 2003 due to severe bronchopneumonia. The organism isolated was Pseudomonas aeruginosa. He was being follow up in Sabah.
8.	DH	Her weighs 8.5 kg with a height of 76 cm. Both his height and weight are below the third centile. After his first infection at three months he developed bronchiolitis obliterans and required home oxygen therapy for six months. His developmental milestones was normal
9	NF	She was ventilated secondary to severe bronchopneumonia. The organism isolated was Pseudomonas aeruginosa
10.	AL	At diagnosis, he was hypoxic in air at 80% saturation. He was prescribed home oxygen therapy. He was follow-up in Sabah since he is from there. However he died in the year 2002 after a few months of diagnosis secondary to severe bronchopneumonia
11.	TG	She is attending standard two. Her weight is 23.9 kg and height of 122 cm at the 50th centiles. She is doing well.
12	SF	She is oxygen dependent on 15 l/min. Since diagnosis she has rapid deterioration of her respiratory status over a period of six months. At the diagnosis she only required 2 l/min. This is secondary to the underlying congenital myopathy. Her weight is only 10.5 kg below the third centiles.
13	BA	He is attending standard three His height is 116 cm and weight of 20,8 kg below the third cnetiles.
14	NDL	His height is 85.2cm and weight of 12.8kg. Both are at the 50th Centiles.
15.	RE	His height is 76cm and weight of 8.3kg. Both parameter are at below the third centiles
16.	MQM	Her weight I 18.1kg and height is 145cm. Both height and weight are below the third centiles. At presentation she was hypoxix in air requiring 10 l/min of oxygen to maintain saturation of 95%. With treatment she improves and the oxygen was reduced to 5l/min. currently she is send back to Sibu since she lives there. She is planned for home oxygen therapy.

Discussion

The gene for CF is located at chromosome 7[4]. It codes the protein cystic fibrosis transmembrane conductance (CFTR), which is a CAMP regulated chloride channel that affects sodium transport. It results in defective chloride secretions and increases sodium absorption in the airway epithelial. This defect results in tenacious secretion in the airways that impairs the airway mucociliary clearance and mucus plugging in the airways. CF is diagnosed by one year old in 80% of children and 8% by eight years old[5]. Half of our patients were diagnosed after one year old. In the west it is diagnosed earlier due to the higher prevalence of this disease and the availability of the screening programme. The panel of consensus[6] recommended that the diagnosis of CF is based on the presence of one or more phenotypic picture of CF, a history of CF in a sibling and elevated sweat chloride of >60 mmol/l or a positive newborn screening test result plus laboratory evidence of a CFTR abnormality as documented by elevated sweat chloride concentration >60 mmol/l, or identification of mutations in each CFTR gene known to cause CF or in vivo demonstration of characteristic abnormalities in ion transport across the nasal epithelium. Currently, we are only able to perform the sweat tests without any gene testing. Due to the lower prevalence of this disease, it will not be cost–effective to screen this disease.

The acceptable sweat chloride test must be conducted using quantitative pilocarpine inotophresis. A minimal of 15 microliter is required using the Wescor Macroduct cell system or 75mg of sweat if using the Gibson and Cooke method. Sweat testing is available only in Pediatric Institute and the University Malaya Medical Centre. In Paediatric Institute we used the Wescor Macroduct coil system. The sweat test must be positive on two separate occasions.

The phenotypic diagnosis of CF is based on the following clinical criteria:

1. Chronic Sino pulmonary disease manifested by:-
a. Persistent colonization/infection with typical CF pathogens including *Staphylococcus aureus, nontypeable Haemophilus influenzae*, mucoid and

nonmucoid *Pseudomonas aeruginosa, and Burkholderia cepacia*
b. Chronic cough and sputum production
c. Persistent chest radiograph abnormalities (e.g., bronchiectasis, atelectasis, infiltrates, hyperinflation).
d. Airway obstruction manifested by recurrent wheezing and air trapping.
e. Nasal polyps; radiographic or computed tomographic abnormalities of the paranasal sinuses.
f. Digital clubbing

2. Gastrointestinal and nutritional abnormalities which include
a. Intestinal: meconium ileus, distal intestinal obstruction syndrome, rectal prolapse
b. Pancreatic: pancreatic insufficiency, recurrent pancreatitis.
c. Hepatic: chronic hepatic disease manifested by clinical or histologic evidence of focal biliary cirrhosis or multilobular cirrhosis
d. Nutritional: failure to thrive (protein-calorie malnutrition), hypoproteinemia and oedema, complications secondary to fat-soluble vitamin deficiency
e. Salt loss syndromes: acute salt depletion, chronic metabolic alkalosis.
f. Male urogenital abnormalities resulting in obstructive azoospermia (CBAVD)

Pancreatic insufficiency is found in 59% of newborns and 80% by the age of one year[7]. 10-20% of CF will present with meconium ileus by 48 hours of presentation. This is due to obstruction of the distal ileum by viscid mucus. Almost all babies with meconium ileus have CF. Therefore all babies presented with meconium ileus require sweat testing. Currently, in our country we are not performing sweat test in all our patients with meconium ileus obstruction since only two centers are providing sweat testing facility. Therefore we may be missing cases of CF in these group of children. Those with late diagnosis as in our patients had established bronchiectasis upon presentation. Studies have shown that the inflammation in the lung may start early in life[8]. The stagnation of secretions leads to chronic bacterial infection and exaggerated immune response, which is responsible for structural damage in the airways and parenchyma. Chronic inflammation of the airways will lead to irreversible changes with the presence of bronchiectasis. It is likely that it will also results in damage to adjacent healthy areas in the lung. Progressive structural damage leads to end stage lung disease[9].

Studies have shown that the thickening of the inner wall as well as increase in the smooth muscle areas of the peripheral airways could contribute to the airflow obstruction and bronchial hyperresponsiveness. Studies have shown that pulmonary function tests may not be sensitive to the detect progression of the disease. Pulmonary function test may be normal in the presence of progressive bronchiectasis detected on the high resolution computed tomograms (HRCT) [10].

Pancreatic[11] replacements are important to prevent fat malabsorption thus improving the nutritional status of these patients. Since these are porcine in origin it is important to explain to our Muslims and Hindu patients. The recommended dosages are 10,000 unit/kg/day adjusted with the meals taken. The enzymes are effective for 30 minutes after consumption. The capsules need to be swallowed. In younger children they can take the granules within the capsule with acidic fruit puree.

Routine physiotherapy is incorporated in their daily routine. Chest physiotherapy[12] is vital during the acute deterioration in lung function and in the maintenance of long-term stability of lung function. Parents are taught to perform chest physiotherapy on their children. For the older children, they are encouraged to be active in any sporting activities that they preferred. Loss of lung function is reportedly more common in young adolescent girls due to their sedentary life as compared to the boys.

Another issue that needs to be addressed is the transition period of childhood, adolescents and adulthood. As this is a chronic disease which worsens overtime it is very important to support them and their family emotionally. There will also be the imminent transfer of care i.e. from the paediatric care to the adult chest physician care. This may not be an easy period and time must be given for these patients to adjust and the transfer must be smooth. They may be a period of overlap where both the paediatric and adult chest physicians will be seeing them to ease the transition period. In the West, there are clinics that were both run by paediatric and adult chest physicians to manage these cases together.

Conclusion

Cystic fibrosis is a chronic disease that worsened with time. In Malaysia there should be an increase in awareness of these disease. Early respiratory management may delay the progression of these disease.

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